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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/560,337

12/09/2005

Valerio Cioli

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EXAMINER

WESTERBERG, NISSA M

ART UNIT

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1618

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DELIVERY MODE

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/560,337	<b>Applicant(s)</b> CIOLI, VALERIO	
	<b>Examiner</b> Nissa M. Westerberg	<b>Art Unit</b> 1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 07 February 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 11 - 21 is/are pending in the application.
- 4a) Of the above claim(s) 14 - 20 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 11 - 13, 21 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>12/9/05</u> .   | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Response to Election/Restriction***

1. Applicant's election with traverse of nimesulide, the absence of an excipient, the absence of a lubricant and the absence of a sweetener in the reply filed on February 7, 2008 are acknowledged. The traversal is on the ground(s) that non-steroidal anti-inflammatory active substances (FANS) are a "well-known omogeneous [sic] class of compounds which has the same or similar pharmacological action" and that the sublingual administration route acts "to considerably reduce ... the administered dosis [sic] for all the FANS". This is not found persuasive because while FANS are a well-known group of compounds, the members of this group are not homogenous in all respects. The structures of the drugs encompassed within the class a very diverse (see for example, diclofenac, nimesulide and ibuprofen) and by Applicant's admission, not all FANS are capable of being absorbed by the oral mucosa (see claim 12). Paracetamol (also known as acetaminophen) is a member of this family that is effective in the treatment of fever and headaches but is not very effective as an anti-inflammatory agent.

The requirement is still deemed proper and is therefore made FINAL.

Claims 14 – 20 are withdrawn from consideration as being drawn to the non-elected invention. The search was not expanded beyond the elected species as art was found against the elected species.

***Claim Rejections - 35 USC § 112 1<sup>st</sup> Paragraph***

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 11 – 13 and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. While the genus of inflammatory symptoms and two specific species, pain and fever, are described, other species within the genus inflammatory symptoms do not meet the written description provision of 35 USC § 112, first paragraph. A number of other symptoms are also encompassed by the genus inflammatory symptoms such as altered immune system function, rashes and swelling and these other species do not meet the written description provision of 35 USC § 112, first paragraph.

***Claim Rejections - 35 USC § 112 2<sup>nd</sup> Paragraph***

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 11 – 13 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. One possible interpretation of this claim is as a method of administering a particular type of pharmaceutical formulation with an intended use of treating inflammatory symptoms. Another interpretation of this claim is as a method of treating inflammatory symptoms wherein the method comprises the step of administering a particular pharmaceutical formulation. These are two distinct methods which require different steps.

6. Claims 11 – 13 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims contain language relating to the relative amounts of active ingredient present in dosage forms of various types. In particular, the dosage in a sublingual formulation and a dosage in an oral formulation. Applicant states on p 1 (ln 15 – 16) of the instant specification that oral administration is the “form of preparations to swallow.” Examples of sublingual dosage forms provided in claim 21 include pressed capsule and pill. As these pharmaceutical forms are also preparations to swallow, it is unclear what dosage form(s) are being compared to the dosage amount present in the sublingual dosage form. It is also unclear what “therapeutic effect” means. For example, the therapeutic effect could be related to general symptom (inflammation, fever or pain) relief, the onset of symptom relief, the

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duration of symptom relief, absence of side effects or various pharmacokinetic parameters of the drug itself such as the area under the curve (AUC),  $C_{\max}$  or  $T_{\max}$ .

7. Claims 11 – 13 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 13 recites the broad recitation "inflammatory symptoms", and the claim also recites "pain" and "fever" which are narrower statement of the range/limitation.

8. Claims 11 – 13 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

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which applicant regards as the invention. The term "drastically" in claim 11 is a relative term which renders the claim indefinite. The term "drastically" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

### ***Claim Rejections - 35 USC § 102***

For the purposes of applying art, the claims of the instant application have been interpreted as a method of administering a particular type of pharmaceutical formulation with an intended use of treating inflammatory symptoms.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 11 – 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Kerouac et al. (WO 99/40898).

Kerouac et al. discloses that sublingual administration of a drug results in rapid absorption of the drug leading to rapid onset of action and avoidance of extensive hepatic degradation (p 1, ln 11 – 13). Drugs can be administered through the mucosal lining of the mouth sublingually (from the area beneath the tongue which is rich in

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vascular and lymphatic vessels) or buccally (from the area between the cheek and gum) (p 1, ln 8 – 10). Example 10 (p 19, ln 28 – 31) discloses sublingual pellets of the non-steroidal anti-inflammatory drugs indomethacin and tenoxicam. In example 1, the sublingual pellets were administered to a subject (p 16, ln 20 – 21). Among the factors that govern a drug dosage regimen are drug bioavailability and drug elimination (p 12, ln 25 – p 13, ln 4). Bioavailability is in part determined by the method of administration (for example, intravenous versus oral, for example; p 13, ln 6 – 12). For drugs that are subject to extensive degradation in the gastrointestinal environment or extensive degradation during their first passage through the liver (hepatic degradation), a sublingual dose will have a much better chance than the same oral dose to distribute throughout the body and exert the therapeutic effect of the drug before it is inactivated (p 14, ln 38 – p 15, ln 4). Thus, the dose of the drug in the sublingual formulation can be lower than that is a dosage form wherein the active ingredient is absorbed by the body in the gastrointestinal tract.

A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim and the compositions of Kerouac et al. comprising the NSAID indomethacin and tenoxicam would be capable of treating inflammation.

***Claim Rejections - 35 USC § 103***

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

12. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. Claims 11 – 13 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kerouac et al. (WO 99/40898) in view of Mehta et al. (WO 01/85134).

Kerouac et al. discloses that sublingual administration of a drug results in rapid absorption of the drug leading to rapid onset of action and avoidance of extensive hepatic degradation (p 1, ln 11 – 13). Drugs can be administered through the mucosal lining of the mouth with sublingually (from the area beneath the tongue which is rich in vascular and lymphatic vessels) or buccally (from the area between the cheek and gum) (p 1, ln 8 – 10). Example 10 (p 19, ln 28 – 31) discloses sublingual pellets of the non-

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steroidal anti-inflammatory drugs indomethacin and tenoxicam. In example 1, the sublingual pellets were administered to a subject (p 16, ln 20 – 21). A granular form (granulate) of the composition is also disclosed (p 21, ln 21 – 22). Among the factors that govern a drug dosage regimen are drug bioavailability and drug elimination (p 12, ln 25 – p 13, ln 4). Bioavailability is in part determined by the method of administration (for example, intravenous versus oral, for example; p 13, ln 6 – 12). For drugs that are subject to extensive degradation in the gastrointestinal environment or extensive degradation during their first passage through the liver (hepatic degradation), a sublingual dose will have a much better chance than the same oral dose to distribute throughout the body and exert the therapeutic effect of the drug before it is inactivated (p 14, ln 38 – p 15, ln 4). Thus, the dose of the drug in the sublingual formulation can be lower than that is a dosage form wherein the active ingredient is absorbed by the body in the gastrointestinal tract.

Kerouac et al. does not exemplify nimesulide as a drug that can be administered through the mucosal lining of the mouth (either buccally or sublingually).

Mehta et al. discloses tablets compositions that comprise a NSAID such as nimesulide that rapidly disintegrate in the buccal cavity (p 1, paragraph 1). Solid tablet or capsules are the most common oral drug administration methods (p 1, paragraph 2). Granulates suitable for the preparations of rapidly disintegrating mouth soluble tablets are known in the art (p 2, last paragraph). Examples 1 (p 6), 3 (p 9) and 4 (p 10) are compositions comprising nimesulide which were administered to adults to determine the disintegration time in the buccal cavity.

A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to administer a sublingual composition of a drug as taught by Kerouac et al. with nimesulide as the active ingredient as Mehta et al. teaches that nimesulide can be absorbed through the mucosal membrane of the mouth. Optimization of the total drug dosage is a results effective parameter which an artisan of ordinary skill would routinely optimize. As sublingual administration results in more rapid absorption and hence more rapid onset of symptom relief and decreases hepatic degradation for drugs subject to such degradation, a lower total drug dosage could result in the same or improved therapeutic effect.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nissa M. Westerberg whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 7:30 a.m. - 5 p.m. ET. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone

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number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/  
Supervisory Patent Examiner, Art Unit 1618

NMW